

**REMARKS**

Applicants respectfully request reconsideration in view of the following remarks. Issues raised in the Office Action are addressed below in the order they were raised by the Examiner.

**Double Patenting**

Claims 2, 9-12, 16, 20, and 24-25 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 3-7, and 9-10 of U.S. Patent No. 6,291,667 in view of Uchida et al. (US Patent No. 6,150,092).

Applicants respectfully request that the Examiner hold this rejection in abeyance until allowable subject matter is found, at which point, Applicants may submit a terminal disclaimer as appropriate.

**Claim Rejections under 35 USC § 103(a)**

The Examiner maintains the rejection of claims 2, 9-12, 16, 20, and 24-25 under 35 USC § 103(a) as allegedly being unpatentable over Uchida et al. (U.S. Pat. No. 6,150,092) in view of Robinson et al. (5,814,620; 5,710,136; and 5,801,156). Applicants respectfully traverse.

Applicants maintain the arguments of record with respect to the combination of references and contend that the combination of references cited by the Examiner fail to disclose the particular combination of elements presently claimed.

Applicants further submit that the claimed invention relates to a few particular VEGF antisense oligonucleotides which are phosphorothioate (PS)-modified. By contrast, Uchida merely teaches SEQ ID NO: 7 as a target VEGF region and some specific oligonucleotides which target this region. The teachings of Uchida at best disclose a genus of VEGF antisense oligonucleotides which target SEQ ID NO: 7, while the claimed invention essentially constitutes a species invention. Applicants submit that this species invention is not obvious in view of Uchida's genus disclosure because Uchida provides no teaching or suggestion to select the claimed species sequences. Thus, one of ordinary skill in the art would have had no motivation

to select the claimed species (SEQ ID NOs: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28 and 29), either in the unmodified form or the modified form.

MPEP 2144.08, Section II.A.4 sets forth the guideline for determining whether a claimed species is obvious in view of a prior art genus: “[i]n light of the findings made relating to the three *Graham* factors, Office personnel should determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, *i.e.*, to select the claimed species or subgenus from the disclosed prior art genus. *See, e.g., Ochiai*, 71 F.3d at 1569-70, 37 USPQ2d at 1131; *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 (‘A prima facie case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art.’ (emphasis in original)); *Jones*, 958 F.2d at 351, 21 USPQ2d at 1943-44 (Fed. Cir. 1992); *Dillon*, 919 F.2d at 692, 16 USPQ2d at 1901; *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) (‘The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.’)... To address this key issue, Office personnel should consider all relevant prior art teachings, focusing on” (where applicable) (a) the size of the genus, (b) the express teachings, (c) the teachings of structural similarity, (d) the teachings of similar properties or uses, (e) the predictability of the technology, and (f) any other teaching to support the selection of the species or subgenus.

Applicants submit that Uchida's genus covers at least thousands of species considering that each antisense oligonucleotide may differ from each other by at least one nucleotide and by length. However, only a few species sequences correspond to the claimed invention. The large size of the genus clearly favors the non-obviousness of the claimed invention.

Applicants submit that Uchida fails to expressly teach any particular reason to select the claimed species, and the Office Action fails to point out any express disclosure which would have motivated one of ordinary skill in the art to select the claimed invention.

Regarding the teachings of similar properties or uses, Applicants submit that it is the instant specification that discloses the unexpected and unique result of achieving substantial

inhibition of cancer cell proliferation in cultured cells and in animal models (see, e.g., Examples 3-7 and 9-11 on pages 19-28).

The predictability of the technology factor also favors non-obviousness in this case. Antisense technology was well known for its unpredictability. Indeed, VEGF antisense oligonucleotides differing by one or two nucleotides exhibit significantly different activity in inhibiting VEGF expression. For example, Uchida's Table 2 shows that although A473J differs from A473I by a single nucleotide, there is an about 50-fold difference in their activities. Also, Applicants' specification discloses that although SEQ ID NOs: 8 and 9 differ by two nucleotides, there is an about 10-fold difference in their activities (see Table 1 on page 24).

The Examiner appears to focus on the "structural similarity" factor. However, considering all the relevant factors, the totality of the circumstances strongly favors the non-obviousness of the claimed species invention. Accordingly, Uchida does not provide one of ordinary skill in the art with the motivation to select and use the claimed antisense probes. Indeed, given that the claimed antisense probes (either unmodified or modified) are not disclosed literally or inherently in Uchida, it is unreasonable to assume that one of ordinary skill in the art could find in the teachings of Uchida any motivation to make these particular sequences and to further modify the oligonucleotides with PS. No other reference cited provides any sequence that is identical or similar to the claimed sequences either modified or unmodified.

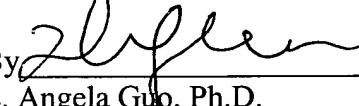
Accordingly, Applicants submit that all of the pending claims are non-obvious in view of Uchida et al. and the defects of Uchida et al. are not cured by the other cited references. Applicants assert that the claims are not obvious in view of all cited references. This conclusion is further corroborated by the previously filed declarations of Drs. Gill and Zhang, two experts in the field of antisense technology. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

**CONCLUSION**

Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000. If there are any fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945**, under **VASG-P02-003**.

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Respectfully submitted,

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